






Fast buccal tablet.**Publication number:** JP4502318 (T)**Publication date:** 1992-04-23**Inventor(s):****Applicant(s):****Classification:**

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Abstract of corresponding document: **EP 0371466 (A1)**

A fast dissolving buccal tablet for administering a medicament includes the active ingredient, a lubricant and a water soluble sugar, such as sorbitol, combined such that the buccal tablet dissolves in about one minute.

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⑪ 公表特許公報(A)

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⑳ 発 明 者 マフカーティ, ジョン・エイ

アメリカ合衆国フロリダ州33161, ビスケイン, ハンドレッドトウ
エンティファースト・ストリート 630 ノース・イースト

㉖ 出 願 人 シェリング・コーポレーション

アメリカ合衆国ニュージャージー州07033, ケニルワース, ギャロ
ツピング・ヒル・ロード 2000

㉗ 代 理 人 弁理士 湯浅 恭三 外6名

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AT(広域特許), AU, BB, BE(広域特許), BF(広域特許), BG, BJ(広域特許), BR, CF(広域特許), CG(広域特許), CH(広域特許), CM(広域特許), DE(広域特許), DK, ES(広域特許), FI, FR(広域特許), GA(広域特許), GB(広域特許), HU, IT(広域特許), JP, KP, KR, LK, LU(広域特許), MC, MG, ML(広域特許), MR(広域特許), MW, NL(広域特許), NO, RO, SD, SE(広域特許), SN(広域特許), SU, TD(広域特許), TG(広域特許)

最終頁に続く

請求の範囲

1. 水性性賦形剤を含む医薬用パツカル錠。
2. パツカル錠の該水性性賦形剤がソルビトールである請求項1記載の医薬用パツカル錠。
3. 医薬上許容しうる賦形剤をさらに含む、請求項1若しくは2のいずれかに記載の医薬用パツカル錠。
4. 該賦形剤がステアリン酸マグネシウム若しくはドデシル硫酸ナトリウムから選択される、請求項3記載の医薬用パツカル錠。
5. 該賦形剤がドデシル硫酸ナトリウムである、請求項1、2若しくは4のいずれかに記載の医薬用パツカル錠。
6. 活性成分としてさらにエストロゲン、プロゲステロン、甲状腺ホルモン、鎮痛剤、エルゴタミン誘導体、プロモクリプテン、pH感受性ペプチド及び小分子量蛋白、フィソステグミン、スコボラミン、ペラバミール若しくはガロバミールを含む、請求項1、2若しくは4記載の医薬用パツカル錠。
7. 活性成分と水性性賦形剤を混合することを含む、医薬用パツカル錠の製造方法。
8. 該水性性賦形剤がソルビトールである、請求項7記載の方法。
9. 医薬上許容しうる賦形剤をさらに混合することを含む、請求項7若しくは8のいずれかに記載の方法。
10. 医薬上許容しうる賦形剤がステアリン酸マグネシウム若しくはドデシル硫酸ナトリウムである、請求項7記載の方法。
11. 該活性成分がエストロゲン、エルゴタミン誘導体、プロモクリプテン、pH感受性ペプチド及び小分子量蛋白、フィソステグミン、スコボラミン、ペラバミール若しくはガロバミールである、請求項7、8若しくは10のいずれかに記載の方法。
12. 実質的に上に述べられている医薬用パツカル組成物。
13. 実質的に上に述べられている医薬用パツカル組成物を製造する方法。

明 細 書

速効性パツカル錠

発明の概要

本発明は、ソルビトールを必須成分とする賦形剤及び潤滑剤と組み合わせた、有効量の活性成分を含むパツカル錠に関する。本錠剤は、予期せぬような非常に迅速な薬物放出をもたらす。活性成分の非経口投与に匹敵する血中濃度を与える。

発明の要旨

本出願は、活性成分のパツカル錠と用剤に関する。他の非注射（経口投与）方式による投与で低いバイオアベイラビリティしか示さない活性成分については（投与対象者の種内の種の中への）パツカル投与は特に有用である。このアベイラビリティの低さは、腸管を通過する際の溶解度の低さや腸管による分解あるいは腸による分解、若しくは胃腸管から吸収された後の肝臓による初期通過分解が原因と考えることができる。このような薬物の例には、エストロゲン、例えばエストラジオール並びにその塩、及びそのバレレート、シビオネート若しくはプロビオネートの形の誘導体、プロゲステロン及び関連化合物等のプロゲステン、アンドロゲン及びステロイド等のステロイド類；プロプラノロール；甲状腺ホルモン；モルヒネ及びモルヒネ誘導体、フェンタニル及びスルフェンタニル等の鎮痛剤；エルゴタミン誘導体（片頭痛治療用）；プロモクリプテン（パーキンソン病治療用）；インシュリン及びACTH等のpH感受性ペプチド及び小分子量蛋白；フィソステグミン；スコボラミン；ペラバミール；及びガロバミールがある。良好な経口バイオアベイラビリティを持つ化合物をパツカル投与することも可能であるが、通常そのような薬物は便宜上経口投与される。

エストラジオールのパツカル投与は非常に早い血中濃度ピークをもたらす。濃度はその後ゆっくりと低下する。これは体内におけるエストラジオールの自然な発現をなぞるものであり、それゆえに比較的一定な血中レベルをもたらす経口投与よりも改善されている。エストラジオール等のエストロゲンの経口投与は、活

性成分が胃腸管から吸収された後直ちに肝臓中で分解されるために実用ではない。

殆どのパッカル処方では、活性成分を持続的に放出させ、それにより投薬形態の崩壊による活性成分の飲み下しを防ぐように設計されている。他のパッカル処方には、パッカル錠の崩壊を早めるように崩壊剤を使用するものがある。そのような崩壊剤には、コーンブラム及びストゥーパック (Kornblum and Stoopak)、ジャーナルオブファーマシューティカルサイエンス (J. Pharm. Sciences)、62巻、第43-49頁、1973年；米国特許第 1,380,171号；カーン及びルーク (Khan and Rooke)、マニファクチャリングケミストアンドエアソールニュース (Mfg. Chemist & Aerosol News)、1976年1月；及びカーン及びルーク (Khan and Rooke)、ジャーナルオブファーマシューティクスアンドファーマコロジー (J. Pharm. Pharmac.)、28巻、第 633-636頁、1976年に開示されているように、ポリビニルポリピロリドン、デンプン、アルギン酸、ホルムアルデヒド、カルボキシメチルセルロースカルシウム、グリコール酸ナトリウムデンプン、及びカルボキシメチルセルロースナトリウムがある。

本発明人は、活性成分をパッカル錠を通して予期せぬほど迅速に放出する速効性パッカル処方を見出した。パッカル処方からのこのような迅速な放出は、血中レベルの急速な上昇をなし速けるための大用量の放出に役立つ。さらに予期せぬことに、該パッカル錠からの薬物の迅速な放出は、他のパッカル錠において患者が投薬形態のまま飲み下すのを防ぐために必要な緩衝剤を不必要にする。そのような緩衝剤含有性パッカル錠は、例えば、米国特許第 4,755,386号、米国特許第 4,050,686号、米国特許第 4,292,299号、及び米国特許第 4,226,848号に開示されている。

発明の詳細な説明

本速効性パッカル処方では以下の3成分を必須成分として含むことができる：パッカル吸収可能な活性成分（薬）、医薬上許容しうる崩壊剤、及び直接圧縮可能な可溶性錠剤用賦形剤。

該可溶性賦形剤は通常、スクロース若しくはラクトース等の糖である。好ましい糖はソルビトール、特に約90ないし99パーセントの範囲の量のソルビトール N

重量%	成分	量
0.2	エストラジオール、USP	2.0 g
98.8	ソルビトール N.F.	988.0 g
1.0	ドデシル硫酸ナトリウム	10.0 g
100.00		

約1000 PSIの圧縮圧を用いて、約0.05 g/錠の重量の錠剤を製造する。本パッチから約20,000錠が得られ、これらは投与時には約1分以内に崩壊する。該錠剤の直径は約1/4 インチである。

実施例2

先の実施例1に述べた方法を用いて、下記の表1に記載する賦形剤を用いてパッカル錠を製造する。各打錠機は、500、1000若しくは2000 psiの圧縮圧で適宜行う。インビトロ崩壊試験の結果では、各処方から約1分以内に崩壊するパッカル錠が製造されることが示されている。下記のソルビトールの量は、活性成分が追加できるように減らされねばならない。例えば、エストラジオールの通常量は0.2重量%であるため、ソルビトールの量は0.2%減らされることになろう。例えばスコポリン等の異なる活性成分を用いる場合、ソルビトールの含有量はそれに応じて減らされる。

ソルビトール N.F. (%)	表1	
	ステアリン酸 マグネシウム (%)	ドデシル硫酸 ナトリウム (%)
98.0	0	2.0
97.0	0	3.0
98.8	0.2	1.0
97.8	0.2	2.0
96.8	0.2	3.0
98.5	0.5	1.0

、P、及び/又はスプレードライドソルビトールである。該可溶性賦形剤には、疎水性活性成分のビヒクルも含まれる。このようなビヒクルには重塩付近で崩壊する固体及び界面活性剤がある。この考え方は、界面活性剤中のミセル可溶化により、あるいは該可溶性薬物をその中に含んだ、体積付近で崩壊する固体を有することにより、若しくはそのような界面活性剤及び固体を組み合わせて用いることにより、不溶性薬物の溶解性を改善するためにこれらのビヒクルを用いるというものである。適当な界面活性剤にはブルコニック、トゥーイン、ラウリル硫酸ナトリウム等があり、適当な崩壊固体には種々のポリエチレングリコール、低融点グリセリド（好ましくは約25ないし45℃の融点を持つ）及び種々の塩基剤があり、これらは当業者に周知である。

本速効性パッカル処方に使用される崩壊剤は、ステアリン酸マグネシウム若しくはドデシル硫酸ナトリウム等の通常量のいずれの崩壊剤でもよい。一般に、崩壊剤は水溶性であることが望ましい。そこで、好ましい崩壊剤は約1ないし3パーセントの範囲の量のドデシル硫酸ナトリウムである。

本発明において有用な活性成分としては発明の背景で述べたものがある。含有量は、所定の治療に対して求められる用量に応じて異なってもよい。活性成分としてエストラジオールを用いる場合は、1錠当たり約50マイクログラムないし約2ミリグラムの範囲の量で用いる。

本発明の処方では、単に成分を合わせて混合し、該混合物を必要量ずつ錠剤形態に圧縮することにより製造することができる。望ましい最終的錠剤は約4分の1インチ (0.635 cm) の直径と約0.05インチ (0.127 cm) の厚みを持ち、投与時には約30秒ないし約5分、好ましくは約1分以内に崩壊するようなものである。

本発明を、以下の非限定例により具体的に説明する。

実施例1

以下の成分を増強パーチV型プレッシャーを用いて混合し、約5ないし10分間混合する。

97.5	0.5	2.0
96.5	0.5	3.0

実施例3

下記の表2に示す賦形剤を含有する処方により、先の実施例中のソルビトール N.F. をスプレードライドソルビトールに代えて実施例1の方法を使用し、約1分以内に活性成分を放出するパッカル錠を製造する。

表2		
スプレードライド ソルビトール (%)	ステアリン酸 マグネシウム (%)	ドデシル硫酸 ナトリウム (%)
98.8	0.2	3.0
97.5	0.5	2.0

上記の処方及び崩壊データに基づけば、ここに述べた速効性パッカル錠はパッカル吸収可能な活性成分を約1分以内にそのような治療が必要な患者に対して放出するであろう。

ここに述べた発明に従って活性成分を投与するには、速効性パッカル錠を口腔内の頬の奥の中に入れて溶解させるだけでよい。薬物は溶解後、全身に放出される。

薬物のこのような迅速な放出は、作用の迅速な開始が求められる場合に特に重要である。例えば、乗り物酔いによる不快感を抑えるためのスコポリンの迅速な投与は好ましい適用の一つである。同時にエストラジオールの迅速な放出は、得られる薬物動態が自然に起こる女性ホルモンの放出と崩壊を模倣するという点において重要である。

本発明の詳細な説明及び幾つかの好ましい形態を上記に示したが、本発明はそれらに限定されるものではなく、むしろ以下の請求の範囲に定義される。

補正書の翻訳文提出書
(特許法第184条の8)

平成 3年 5月 30日

特許庁長官 樋 松 敏 殿

1. 特許出願の表示

PCT/US89/05260

2. 発明の名称

速効性パッカル錠

3. 特許出願人

住 所 アメリカ合衆国ニュージャージー州07033,
ケニルワース、ギャロピング・ヒル・ロード 2000
名 称 シェリング・コーポレーション

4. 代理人

住 所 東京都千代田区大手町二丁目2番1号
新大手町ビル 206区
電 話 (3270) 6641-8646
氏 名 (2770) 弁理士 湯 浅 恭 三

5. 補正書の提出日

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6. 添付書類の目録

(1) 補正書の翻訳文

1通



5. 該調剤がドデシル硫酸ナトリウムである、請求項4記載の医薬用パッカル錠。

6. 活性成分としてさらにエストロゲン、プロゲステロン、甲状腺ホルモン、鎮痛剤、エルゴタミン誘導体、プロモクリプチン、pH感受性ペプチド及び小分子量蛋白、フィソスチグミン、スコポラミン、ペラバミール若しくはガロバミールを含む、請求項1記載の医薬用パッカル錠。

11. 該活性成分がエストロゲン、エルゴタミン誘導体、プロモクリプチン、pH感受性ペプチド及び小分子量蛋白、フィソスチグミン、スコポラミン、ペラバミール若しくはガロバミールである、請求項7記載の方法。

国際調査報告

PCT/US 89/05260

I. CLASSIFICATION OF SUBJECT MATTER		
According to International Patent Classification (IPC) or to both International Classification and IPC		
Int.Cl. 5 A61K47/26 ; A61K9/20		
II. PRIORS SEARCHED		
Classification System		
Int.Cl. 5	A61K	
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁾		
Category ²⁾	Character of Document ³⁾ and Information, where appropriate, of the reference document ⁴⁾	Reference to Class No. of
X	FR,A,2175853 (PFIZER CORP.) 26 October 1973 see the whole document	1-4, 7-10, 12, 13
A	GB,A,2188843 (RECKITT AND COLMAN PRODUCTS LTD) 14 October 1987 see claims	1-13
A	WO,A,8704342 (KEY PHARMACEUTICALS INC.) 30 July 1987 see claims & US,A,4755386	1-13
<p>¹⁾ Special categories of cited documents:</p> <p>²⁾ "X" documents defining the present state of the art which is an indication of the prior art.</p> <p>³⁾ "A" documents published after the international filing date in which it is stated that the publication date of the document is later than the priority date.</p> <p>⁴⁾ "X" documents published after the international filing date in which it is stated that the publication date of the document is later than the priority date.</p> <p>⁵⁾ "A" documents published after the international filing date in which it is stated that the publication date of the document is later than the priority date.</p> <p>⁶⁾ "X" documents published after the international filing date in which it is stated that the publication date of the document is later than the priority date.</p> <p>⁷⁾ "A" documents published after the international filing date in which it is stated that the publication date of the document is later than the priority date.</p> <p>⁸⁾ "X" 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IV. CERTIFICATION		
This is the Official Certification of the International Bureau		Date of Mailing of the International Search Report
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